

Sex Differences in Blood Pressure and Its Relationship to Body Composition and Metabolism in Adolescence

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Objectives: To investigate during adolescence (1) sex differences in blood pressure (BP) and hemodynamic factors at rest and during physical and mental challenges and (2) whether these differences are mediated by body composition and glucose and lipid metabolism.

Design: Cross-sectional study of a population-based cohort.

Setting: Saguenay Youth Study, Quebec, Canada, from November 2003 to June 2007.

Participants: A total of 425 adolescents (225 girls aged 12-18 years).

Outcome Measures: Systolic and diastolic BP measured using a Finometer. Secondary outcome measures were (1) hemodynamic parameters also measured with a Finometer, (2) body composition assessed with magnetic resonance imaging, bioimpedance, and anthropometry, and (3) metabolic indices determined from a fasting blood sample.

Results: Girls vs boys demonstrated lower systolic and diastolic BP at rest and during challenges, with the differences being greatest during a math-stress test (adjusted difference, 7 mm Hg; 95% confidence interval [CI], 4-10 mm Hg and adjusted difference, 6 mm Hg; 95% CI, 4-8 mm Hg, respectively). The differences were mainly due to girls vs boys having lower stroke volume while lying down, standing (adjusted difference, 4 mL; 95% CI, 1-7 mL), and sitting, and lower total peripheral resistance during the math-stress test (adjusted difference, 0.14 mm Hg·s/mL; 95% CI, 0.09-0.21 mm Hg·s/mL). Intra-abdominal fat was positively associated with BP, but less in girls than in boys, and fat-free mass, fat mass, and insulin resistance were also positively associated with BP, similarly in boys and girls.

Conclusions: In adolescence, BP is lower in girls than boys, with the difference being determined mainly by lower stroke volume during physical challenges and by lower total peripheral resistance during mental challenges. Body composition and insulin resistance contribute to these differences.

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BLOOD PRESSURE (BP) AND the prevalence of hypertension are higher in men than women throughout their reproductive life.¹ Blood pressure underlying hemodynamic parameters also differs between men and women, as does the response to antihypertensive therapy, which shows a lesser benefit for women than men in heart disease prevention.²

Blood pressure varies with parameters of body composition and glucose and lipid metabolism. Some of these parameters show marked sex differences. For example, intra-abdominal adiposity, which is positively associated with BP,^{3,4} is greater in men than women.⁵ Likewise, dyslipidemia that frequently cooccurs with hypertension has a higher prevalence in men than in women.⁶

The aim of this study was (1) to investigate sex differences in BP and underlying hemodynamic parameters and (2) to examine whether parameters of body composition and glucose and lipid metabolism influence these differences in adolescence, when sex differences in BP first emerge.^{4,7,8}

METHODS

SUBJECTS

Female (n=225) and male (n=200) white adolescents aged 12 to 18 years were recruited in the Saguenay-Lac St Jean region of Canada as part of the Saguenay Youth Study.⁹ This is an ongoing investigation of the long-term consequences of prenatal exposure to maternal cigarette smoking on cardiovascular and metabolic health and on brain and behavior in adolescence.⁹ Recruitment and selection cri-

teria have been described previously.^{4,9} Briefly, subjects were recruited via local high schools. All subjects who were exposed prenatally to maternal cigarette smoking, willing to participate, and free of any exclusionary criteria were included in the study. The exclusion criteria were positive medical history of heart disease requiring surgery and/or medication, diabetes mellitus treated with insulin, meningitis, malignancy, severe mental illness (eg, autism, schizophrenia), mental retardation (intelligence quotient <70), or magnetic resonance imaging contraindications.⁹ An equal number of willing and eligible non-exposed subjects were matched to the exposed ones by maternal education (as a proxy of socioeconomic status) and school attended. With this ascertainment, the current Saguenay Youth Study cohort is representative of the French Canadian adolescent population, except for the higher proportion of subjects exposed prenatally to maternal cigarette smoking (50% in the current sample vs 25% in the general population) and, associated with this fact and the matching of the nonexposed subjects to the exposed ones, overrepresentation of families with lower socioeconomic status. Written consent of the parents and assent of the adolescents were obtained before the commencement of data collection. The research ethics committee of the Chicoutimi Hospital approved the study protocol. The current sample consists of subjects recruited and tested between November 2003 and June 2007 (n=508), among whom 425 had complete quality-controlled cardiovascular data sets and were analyzed in the present study.

QUANTITATIVE PHENOTYPING

Cardiovascular Measurements

All subjects underwent a 53-minute cardiovascular protocol conducted in the Chicoutimi hospital on Saturdays between 8 AM and 12 PM. The protocol included changes in posture from supine to standing and from standing to sitting (posture test) and a math-stress test.¹⁰ Throughout the protocol a noninvasive hemodynamic monitor, Finometer (Finapres, Amsterdam, The Netherlands), was used to continuously record finger blood flow. From this data, the Finometer derives beat-to-beat brachial systolic, diastolic, and mean BP and interbeat interval from the reconstructed and level-corrected waveform. The derivation of stroke volume relies on the Modelflow method.¹¹ Heart rate (the inverse of the interbeat interval), cardiac output (the product of stroke volume and heart rate), and total peripheral resistance (mean BP divided by cardiac output) were all calculated. One-minute averages for each parameter were calculated throughout the protocol.

Body Composition and Adiposity

Measurements included weight, height, waist circumference, and multifrequency bioimpedance analysis to estimate total body fat mass and fat-free mass (Xitron Technologies, Inc, San Diego, California). Subjects were asked to refrain from caffeine, alcohol, and vigorous activity for 24 hours before the measurements. A 10-mm thick axial T1-weighted magnetic resonance image at the level of the umbilicus was segmented into intra-abdominal and subcutaneous fat.^{4,9}

Biochemical Analyses

A fasting blood sample was drawn between 8 AM and 9 AM. Serum levels of glucose, insulin, triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were attained. We calculated the homeostasis model assessment (HOMA), an index of insulin resistance using the equation

$HOMA = (\text{glucose in milligrams per deciliter}) \times (\text{insulin in microunits per milliliter}) / 405$ [to convert glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945].¹²

Questionnaires

Subjects completed a questionnaire to evaluate stage of pubertal development using The Puberty Development Scale.¹³ Parents completed questionnaires detailing household income and maternal education as indices of socioeconomic status.

STATISTICAL METHODS

Potentially Confounding Variables

In all multivariable analyses, we adjusted for 6 variables identified as potential confounders of differences between girls and boys in BP, hemodynamic parameters, body composition, and glucose and lipid metabolism: the child's age, height, household income in the year prior to subject examination, maternal education level (9 indicator variables for the 10 stages), puberty stage (4 indicator variables for the 5 stages), and prenatal exposure to maternal cigarette smoking (any or none). In all analyses, we log-transformed household income to normalize its distribution.

Sex Differences in Body Composition and Glucose and Lipid Metabolism

Differences between girls and boys in fat mass, fat-free mass, waist circumference, intra-abdominal fat, subcutaneous abdominal fat, glucose, insulin, insulin resistance (HOMA), triglycerides, HDL-cholesterol, and total cholesterol were tested with 1-way analyses of covariance, with the 6 above potentially confounding variables included in the model. We log-transformed intra-abdominal fat to normalize its distribution. To assess the potential nonlinearity of the associations of the 3 continuous covariates (age, height, and log[household income]), both their linear and quadratic terms were first entered into the model. We then used a backward elimination procedure (with a cut-off of $P > .05$) to eliminate non-statistically significant quadratic associations. Height had a statistically significant quadratic association with fat-free mass and log(intra-abdominal fat), and no other statistically significant quadratic relationships were identified (data not shown). Thus, in the final models, while testing differences between girls and boys for each of the 11 variables, we adjusted for log (household income) (linear term), age (linear term), maternal education, puberty stage, prenatal exposure to maternal cigarette smoking, and either the quadratic associations of height (when statistically significant for a given outcome) or its linear associations. Results are presented as the adjusted differences between the mean values of girls and boys with 95% confidence intervals (CI).

Sex Differences in BP and Hemodynamic Parameters

We tested for sex differences in the repeated-measures 1-minute means of systolic and diastolic BP and 4 hemodynamic factors that determine BP: heart rate, stroke volume, cardiac output, and total peripheral resistance. Heart rate and stroke volume determine cardiac output that, together with total peripheral resistance, determine BP. To account for correlation between consecutive observations in the same subject, we used multivariable mixed linear models, assuming an autoregressive or-

Table 1. Characteristics of Study Adolescents

Characteristic	Mean (SD)		Difference (95% CI) ^a	P Value
	Girls (n=225)	Boys (n=200)		
Age, y	14.7 (1.9)	14.6 (1.9)	0.1 (-0.3 to 0.5)	.58
Height, cm	160.8 (6.7)	167.7 (10.6)	-7.0 (-8.6 to -5.3)	<.001
Tanner stage (1-5)	4.1 (0.7)	3.5 (0.9)	0.66 (0.51 to 0.81)	<.001
Household income, Canadian \$	54 819 (23 398)	53 850 (22 974)	969 (-3481 to 5419)	.67
Log(household income), Canadian \$	10.79 (0.54)	10.77 (0.53)	0.007 (-0.04 to 0.06)	.78
Maternal education (1-10 y)	4.82 (1.45)	4.59 (1.38)	0.22 (-0.05 to 0.50)	.11
Exposed to prenatal smoking, proportion	0.50	0.46	0.04	.44

Abbreviation: CI, confidence interval.

^aDifference calculated as girls - boys.

der 1 covariance structure of residuals.^{14,15} Again, we first entered the aforementioned 6 potentially confounding variables, with quadratic terms for age, height, and log(household income) in the models, and then used a backward elimination procedure (with $P > .05$ cut-off) to eliminate statistically non-significant quadratic associations. We observed that age had statistically significant quadratic associations with systolic BP, heart rate, stroke volume, and total peripheral resistance. Height had statistically significant quadratic associations with heart rate and stroke volume, while log(household income) did not have statistically significant quadratic associations with any of the cardiovascular parameters (data not shown). In all subsequent analyses, we adjusted for log(household income) (linear term), maternal education, puberty stage, prenatal exposure to maternal cigarette smoking, and either the quadratic associations of age and height (when they were significant for specific cardiovascular parameters, as described above) or, otherwise, for their linear associations.

The 53 repeated-measures 1-minute means of the 6 cardiovascular parameters were grouped into 7 sections corresponding to the following experimental conditions: supine, standing, sitting, stress-test explanation, prestress, stress, and stress recovery. Because some parameters may vary between boys and girls depending on an experimental condition, we tested the overall interaction between female sex and protocol sections with a Wald test ($df, 6$). Thus, each mixed model included a binary indicator of female sex, a series of binary indicators of protocol sections, their 2-way interactions with sex, and the appropriate (either linear or linear and quadratic) effects of the 6 aforementioned potentially confounding variables. In the case of statistically significant interactions between female sex and section ($P < .05$ for the Wald test), we estimated protocol section-specific associations with female sex based on the model with all interactions and used the model-based covariance matrix to estimate the corresponding 95% CIs. Hypotheses regarding either the overall effect of female sex (if no significant interaction between female sex and sections) or section-specific sex effects were tested using 2-tailed Wald tests with 1 df ; $P < .05$ were considered significant.

Relationships of Body Composition and Glucose and Lipid Metabolism to Sex Differences in BP

We examined the possible associations with BP of a subset of the 11 variables that potentially influence BP: fat-free mass, fat mass, log(intra-abdominal fat), insulin resistance, triglycerides, HDL-cholesterol, and total cholesterol. Waist circumference and subcutaneous abdominal fat were not included, as we considered log(intra-abdominal fat) a more precise index of central adiposity. Homeostasis model assessment was selected as

an index of insulin resistance instead of fasting insulin. We first tested if each of these 7 variables had linear or quadratic relationships with systolic and diastolic BP in models that included female sex and the 6 potential confounders (with linear or quadratic associations, as determined above).

Next, female sex, the 6 confounding variables (linear or quadratic, as appropriate), and 1 of the 7 variables that potentially influence BP (linear or quadratic, as appropriate) were entered into separate models for systolic and diastolic BP. This was done to assess if, after adjusting for a given factor that potentially influences BP, the mean adjusted difference in BP between girls and boys is still important (clinically or statistically). These analyses considered 1 additional factor at a time to avoid multicollinearity problems and aimed at identifying which variables may mediate the sex difference in BP. We considered a change in the estimated sex difference of BP of 0.5 mm Hg or more to be clinically meaningful.

Finally, we attempted to assess if the associations between each of these 7 factors and BP differs in girls vs boys. To this end, we added the interaction(s) between female sex and either linear or linear and quadratic effects of a given factor to the factor-specific model discussed above. If the interaction with female sex was statistically significant, we relied on the interaction model to reconstruct the separate associations of a given factor for girls vs boys and on the covariance matrix to estimate the corresponding 95% CIs.

All mixed models were performed with the SAS statistical software package, with mixed models implemented in the procedure Mixed (SAS Institute Inc, Carey, North Carolina).

RESULTS

CHARACTERISTICS OF STUDY ADOLESCENTS

Girls and boys did not statistically significantly differ in mean age, household income, maternal education level, or prenatal exposure to maternal cigarette smoking status (**Table 1**). Girls were at a more advanced stage of pubertal development and were, on average, shorter than boys by 7 cm (Table 1).

In terms of body composition, girls had less fat-free mass (by 3.3 kg) and more fat mass (by 2.3 kg) than boys after adjusting for potentially confounding variables including age, height, and pubertal development (**Table 2**). Girls, compared with boys, also demonstrated smaller waist circumference (by 1.6 cm) and a greater volume of subcutaneous abdominal fat by 20 cm³, but they had

Table 2. Sex Differences in Body Composition and Glucose and Lipid Metabolism

	Mean (SD)		Difference in Adjusted Means (95% CI) ^a	P Value
	Girls (n=225)	Boys (n=200)		
Fat-free mass, kg	41.6 (4.7)	51.7 (10.8)	-3.3 (-4.0 to -2.6)	<.001
Fat mass, kg	14.0 (6.8)	9.7 (6.1)	2.3 (1.5 to 3.1)	<.001
Waist circumference, cm	69.6 (8.3)	73.6 (10.0)	-1.6 (-2.8 to -0.5)	.004
Intra-abdominal fat, mm ³	23 949 (17 784)	25 018 (25 186)	-358 (-3107 to 2392)	.80
Log(intra-abdominal fat, mm ³)	9.84 (0.71)	9.72 (0.89)	0.09 (-0.01 to 0.20)	.07
Subcutaneous fat, mm ³	131 002 (85 960)	88 189 (80 159)	20 762 (10 220 to 31 304)	<.001
Body mass index ^b	21.4 (3.7)	21.5 (3.9)	-0.3 (-0.7 to 0.2)	.24
Glucose, mg/dL	83.4 (7.1)	86.1 (8.0)	-1.1 (-2.9 to 0.9)	.28
Insulin, μ IU/mL	11.8 (4.6)	10.2 (5.6)	2.3 (1.0 to 3.6)	<.001
HOMA	2.37 (1.01)	2.11 (1.23)	0.43 (0.15 to 0.71)	.003
Triglycerides, mg/dL	92 (36)	87 (37)	3 (-6 to 12)	.52
HDL cholesterol, mg/dL	59.5 (12.4)	53.7 (10.6)	5.0 (1.9 to 7.7)	<.001
Total cholesterol, mg/dL	166 (28)	156 (30)	7 (-1 to 14)	.08

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; HOMA, homeostasis model assessment.

SI conversion factors: to convert glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, 6.945; triglycerides to millimoles per liter, 0.0113; total and HDL cholesterol to millimoles per liter, 0.259.

^aDifferences in adjusted means between girls and boys (girls - boys) were calculated in models that included 6 potentially confounding variables: age, height (always a linear term except for log[intra-abdominal fat] and fat-free mass, with which it had a significant quadratic relationship), pubertal development, prenatal exposure to maternal cigarette smoking, household income, and maternal education.

^bCalculated as weight in kilograms divided by height in meters squared.

similar volumes of intra-abdominal fat (Table 2), which suggests that the sex difference in waist circumference is determined by differences in tissues other than adipose tissues. Girls and boys did not statistically significantly differ in body mass index (calculated as weight in kilograms divided by height in meters squared; mean, 21 for both) (Table 2). The range of body mass index was 14 to 34; 14% (28 of 200) of boys and 10% (22 of 221) of girls were obese, as they had body mass indexes above the age- and sex-specific 95th percentile.¹⁶

Regarding glucose metabolism, girls and boys had similar fasting plasma glucose levels (83 and 86 mg/dL, respectively), but girls were more insulin resistant, as indicated by statistically significantly higher fasting plasma insulin and HOMA indexes, by 2.3 and 0.43 μ IU/mL, respectively (Table 2). With respect to lipid metabolism, girls and boys did not differ significantly, except in HDL-cholesterol, which was higher in girls by 5.0 mg/dL (to convert to millimoles per liter, multiply by 0.259) (Table 2).

BP AND HEMODYNAMIC PARAMETERS IN ADOLESCENT GIRLS AND BOYS

On average over the entire protocol, girls compared with boys showed lower mean systolic and diastolic BP by 4.1 (95% CI, 2.1-6.0) mm Hg and 4.6 (95% CI, 3.2-6.0) mm Hg, respectively. Girls vs boys had, on average, higher heart rates by 2.8 (95% CI, 1.6-4.0) beats per minute (bpm), lower stroke volume (by 2.9 [95% CI, 0.9-5.0] mL), and total peripheral resistance (by 0.06 [95% CI, 0.02-0.10] mm Hg·s/mL), but had similar levels of cardiac output (**Figure** and **Table 3**).

These sex differences in BP and hemodynamic parameters varied in size according to the protocol section, as evidenced by statistically significant interactions between section and female sex ($P < .001$ for a 6-*df* test for

all parameters). Although mean values of systolic and diastolic BP were lower in girls than boys throughout the protocol, the differences were greatest during the math-stress test (7.0 [95% CI, 4.4 to 9.7] and 6.0 [95% CI, 4.3 to 7.8] mm Hg, respectively) and smallest during the supine section (1.4 [95% CI, -2.2 to 4.9] and 3.2 [95% CI, 0.9 to 5.5] mm Hg, respectively) (Figure and Table 3). With respect to hemodynamic parameters, heart rate was mostly higher in girls than boys, with the difference ranging from 5.3 [95% CI, 3.5 to 7.2] bpm during the math-stress test to 1.5 [95% CI, -0.9 to 4.0] bpm during the 10-minute standing section. Stroke volume was lower in girls than in boys during the posture test (supine, standing, and sitting) by about 4 mL. Cardiac output, the product of stroke volume and heart rate, did not differ significantly between sexes throughout the protocol, except while standing, when it was lower in girls than boys by 0.36 [95% CI, 0.12 to 0.59] L/min. Total peripheral resistance was lower in girls than boys during the math-stress test (explanation, math-stress test, and recovery) by about 0.1 mm Hg·s/mL, with the difference being greatest during the test 0.15 (95% CI, 0.09 to 2.1) mm Hg·s/mL (Figure and Table 3).

Taken together, BP was lower in girls than boys throughout the entire protocol. This difference was mainly owing to girls having lower mean stroke volume during the posture test and lower mean total peripheral resistance during the math-stress test compared with boys.

RELATIONSHIPS OF BODY COMPOSITION AND METABOLISM TO SEX DIFFERENCES IN BP

We examined whether various parameters of body composition (fat mass, fat-free mass, and intra-abdominal adiposity) and metabolism (HOMA [an index of insulin resistance] and lipid profile) related to BP and its differences

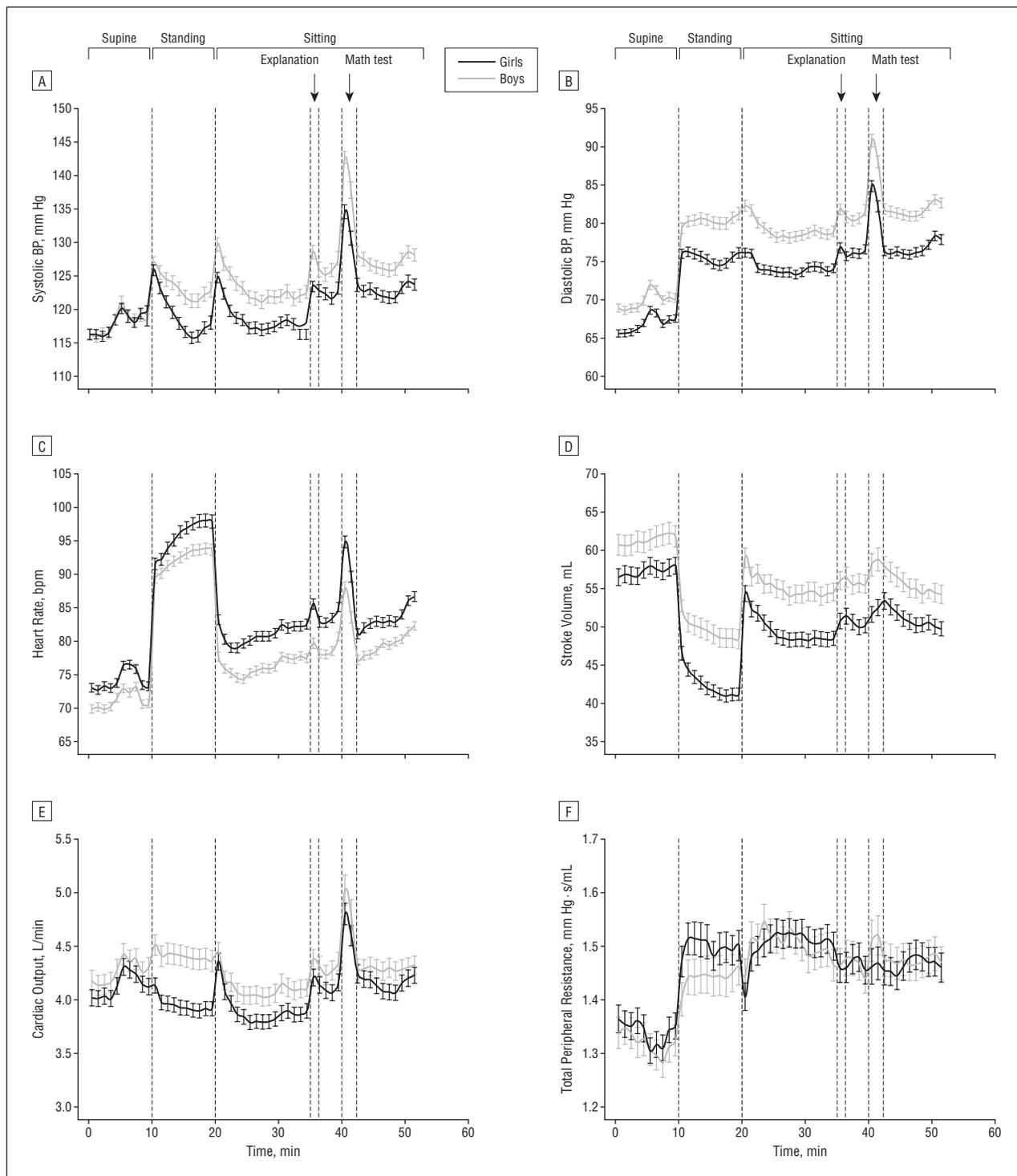


Figure. Blood pressure and underlying hemodynamic parameters. Unadjusted 1-minute means and standard errors of the mean of systolic (A) and diastolic (B) blood pressure (BP), heart rate (in beats per minute [bpm]) (C), stroke volume (D), cardiac output (E), and total peripheral resistance (F) are shown for girls and boys during a 53-minute cardiovascular protocol that includes postural and mental challenges. Adjusted estimated differences between girls and boys for each of the 7 sections are provided in Table 3.

between girls and boys. Fat mass, fat-free mass, and insulin resistance showed statistically significant positive linear associations with systolic and diastolic BP (**Table 4**). More specifically, these results showed that, for 2 hypothetical individuals of either sex who do not differ by any of the potentially confounding variables (age, height, puberty stage, etc), a difference of either +10 kg

of fat-free mass, +16 kg of fat mass, or +2.22 units of HOMA is associated with a mean difference in systolic BP of +4 mm Hg. As boys have more fat-free mass, additionally adjusting for fat-free mass decreased the sex difference in systolic BP from 4.1 (95% CI, 2.1-6.0) (boys > girls) to 2.1 (95% CI, -0.2 to 4.3) mm Hg. As girls have greater fat mass and insulin resistance, additional adjust-

Table 3. Sex Differences in Blood Pressure and Hemodynamic Parameters^a

Outcome	Differences in Adjusted Means by Protocol Section (95% CI) ^b						
	Supine	Standing	Sitting	Explanation	Pretest	Test	Recovery
Systolic BP, mm Hg	-1.4 (-4.9 to 2.2)	-3.8 (-7.3 to -0.4)	-5.0 (-8.3 to -1.7)	-6.0 (-9.2 to -2.9)	-4.6 (-7.5 to -1.7)	-7.0 (-9.7 to -4.4)	-5.7 (-7.9 to -3.4)
Diastolic BP, mm Hg	-3.2 (-5.5 to -0.9)	-3.8 (-6.1 to -1.5)	-5.1 (-7.2 to -2.9)	-5.4 (-7.4 to -3.3)	-5.2 (-7.1 to -3.3)	-6.0 (-7.8 to -4.3)	-5.7 (-7.3 to -4.2)
Heart rate, bpm	2.4 (-0.1 to 4.9)	1.5 (-0.9 to 4.0)	3.2 (0.8 to 5.5)	3.7 (1.4 to 6.0)	3.0 (0.8 to 5.1)	5.3 (3.5 to 7.2)	3.3 (1.8 to 4.7)
Stroke volume, mL	-3.9 (-6.9 to -0.8)	-4.3 (-7.3 to -1.3)	-3.1 (-6.0 to -0.2)	-2.6 (-5.4 to 0.1)	-2.2 (-4.7 to 0.4)	-1.3 (-3.7 to 1.1)	-1.6 (-3.8 to 0.7)
Cardiac output, L/min	-0.17 (-0.41 to 0.07)	-0.36 (-0.59 to -0.12)	-0.07 (-0.30 to 0.15)	-0.06 (-0.27 to 0.16)	-0.05 (-0.25 to 0.16)	0.07 (-0.11 to 0.26)	0.01 (-0.15 to 0.17)
Total peripheral resistance, mm Hg · s/mL	-0.03 (-0.10 to 0.05)	0.03 (-0.05 to 0.10)	-0.07 (-0.15 to -0.003)	-0.09 (-0.16 to -0.02)	-0.10 (-0.16 to -0.03)	-0.15 (-0.21 to -0.09)	-0.11 (-0.16 to -0.06)

Abbreviations: BP, blood pressure; bpm, beats per minute; CI, confidence interval.

^aFemale sex had statistically significant interactions ($P < .001$) with protocol section for each of the 6 hemodynamic variables in mixed models that included a binary indicator of female sex, a series of binary indicators of protocol sections and their interaction, and 6 potentially confounding variables: log(household income), maternal education, puberty stage, prenatal exposure to maternal cigarette smoking, and either the quadratic or linear terms for age, as appropriate (quadratic terms for systolic BP, heart rate, stroke volume, and total peripheral resistance), and height (quadratic for heart rate and stroke volume). We estimated protocol section-specific associations with female sex based on the model with all interactions and used the model-based covariance matrix to estimate the corresponding 95% CIs. Hypotheses regarding the section-specific sex effects were tested using 2-tailed Wald tests ($df, 1$; significant at $P < .05$).

^bDifferences calculated as girls – boys.

ing for these factors (separately) enhanced the sex difference in systolic BP from 4.1 (95% CI, 2.1 to 6.0) (boys > girls) to 6.1 (95% CI, 4.0 to 8.2) and 4.6 (95% CI, 2.6 to 6.5) mm Hg, respectively (**Table 5**). Similar but less pronounced results were observed for diastolic BP (Table 5).

Log(intra-abdominal fat) showed a statistically significant quadratic and linear relationships with systolic BP and a linear relationship with diastolic BP (Table 4). For systolic BP, adjusting for intra-abdominal fat reduced the sex difference in systolic BP from 4.1 (95% CI, 2.1 to 6.0) to 3.6 (95% CI, 1.6 to 5.5) mm Hg. For diastolic BP, adjusting for intra-abdominal fat did not change the sex difference (Table 5).

Next, we tested whether each of the 7 factors that potentially influence BP have a different association with BP in girls than boys. Only log(intra-abdominal fat) showed linear and quadratic associations with systolic BP that both had statistically significant interactions with female sex ($P = .007$ and $.01$, respectively) (**Table 6**). These results suggest that as log(intra-abdominal fat) increases, and thus as intra-abdominal fat itself increases, the sex difference in systolic BP (girls < boys) becomes greater. For example, if a boy and girl who each had 10 cm³ of intra-abdominal fat and who did not differ in systolic BP were instead each to have 30 cm³ of intra-abdominal fat, both would have greater systolic BP, but the boy's systolic BP would now be higher than the girl's by 4 mm Hg. No other factors had statistically significant interactions with female sex (data not shown).

COMMENT

The results of the current study suggest that in adolescence (1) girls, compared with boys, demonstrate lower BP, with the differences being most pronounced during the math-stress test; (2) the sex difference in BP is driven

Table 4. Relationships Between Body Composition and Blood Pressure

Variables	Estimate (95% CI) ^a	
	SBP	DBP
Fat-free mass, kg	0.41 (0.24 to 0.58)	0.32 (0.20 to 0.44)
Fat mass, kg	0.25 (0.11 to 0.38)	0.15 (0.06 to 0.24)
Log(intra-abdominal fat, mm ³)	-23 (-42 to -4)	0.95 (0.17 to 1.73)
Log(intra-abdominal fat, mm ³) ²	1.25 (.28 to 2.22)	Not tested
Insulin resistance, HOMA	1.80 (1.04 to 2.56)	1.11 (0.57 to 1.65)
Triglycerides, mg/dL	6 (-199 to 187)	-21 (-57 to 116)
HDL cholesterol, mg/dL	-30 (-138 to 77)	5 (-72 to 82)
Cholesterol, mg/dL	-7 (-51 to 35)	-20 (-51 to 10)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; SBP, systolic blood pressure.

SI conversions: to convert triglycerides to millimoles per liter, multiply by 0.0113; total and HDL cholesterol to millimoles per liter by 0.259.

^aThe parameters were each tested in separate models that included sex and potentially confounding variables (log[household income], maternal education, puberty stage, prenatal exposure to maternal cigarette smoking, and either the quadratic associations of age and height [when they were significant for specific cardiovascular parameters] or, otherwise, for their linear associations). There was no statistically significant quadratic association of log(intra-abdominal fat) with diastolic BP; thus, an estimate was not calculated. None of the other parameters had statistically significant quadratic associations with either SBP or DBP. Significant associations with BP are in boldface.

mainly by lower stroke volume while lying down, standing, and sitting, and by lower total peripheral resistance during and after mental challenges such as the math-stress test; and (3) intra-abdominal fat is positively associated with BP, less in girls than in boys, and fat-free mass, fat mass, and insulin resistance are also positively associated with BP, but similarly in girls and boys. These relationships, together with the sex differences in body composition and metabolism, contribute to the observed sex differences in BP.

Table 5. Adjusted Estimates of Sex Differences in Systolic and Diastolic Blood Pressure

	Difference in Adjusted Means (95% CI) ^a	
	SBP	DBP
Model 1	-4.1 (-6.0 to -2.1)	-4.6 (-6.0 to -3.2)
Model 1 + fat-free mass	-2.1 (-4.3 to 0.2)	-2.5 (-4.1 to -1.0)
Model 1 + fat mass	-6.1 (-8.2 to -4.0)	-5.7 (-5.1 to -4.2)
Model 1 + log(IAF)	Not tested	-4.4 (-5.8 to -3.0)
Model 1 + log(IAF) + log(IAF) ²	-3.6 (-5.5 to -1.6)	Not tested
Model 1 + insulin resistance	-4.6 (-6.5 to -2.6)	-4.8 (-6.3 to -3.4)
Model 1 + triglycerides	-3.9 (-5.9 to -2.0)	-4.5 (-5.9 to -3.1)
Model 1 + HDL cholesterol	-4.0 (-6.0 to -2.0)	-4.6 (-6.0 to -3.2)
Model 1 + cholesterol	-4.0 (-6.0 to -2.1)	-4.6 (-6.0 to -3.2)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IAF, intra-abdominal fat; SBP, systolic blood pressure.
^aDifferences in adjusted means calculated as girls – boys. Model 1 included only confounding variables (height, pubertal stage, exposure to maternal cigarette smoke, log[household income], maternal education, and age (quadratic term for systolic BP and linear term for diastolic BP)). Each other parameter was added (1 by 1) to model 1 to test its influence on the sex difference in BP. We defined a significant change in the sex difference of BP to be a change of 0.5 mm Hg. Significant changes are in boldface.

Table 6. Relationships of Log(IAF) With SBP

Interaction	SBP Estimate (95% CI)
Log(IAF)	-63.9 (-98.1 to -29.6)
Log(IAF) ²	3.2 (1.5 to 4.9)
Log(IAF) × female sex	-55.1 (-95.4 to -14.8)
Log(IAF) ² × female sex	2.6 (0.6 to 4.7)

Abbreviations: CI, confidence interval; IAF, intra-abdominal fat; SBP, systolic blood pressure.

Body composition changes profoundly during adolescence; girls increase mainly in fat mass, whereas boys enhance mostly fat-free mass.¹⁷ This is consistent with our results demonstrating that girls compared with boys showed more fat mass and less fat-free mass. We observed that both fat-free mass and fat mass were positively associated with BP. It is well known that anthropometric measures of body size such as height^{18,19} relate positively to BP in childhood and adolescence. In the current study, BP relationships to fat-free mass and fat mass were evident after adjustment for height. A positive relationship of BP with fat-free mass in adolescence has been seen previously.²⁰ The mechanisms underlying this relationship are not very well understood. In adolescence, fat-free mass is positively related to plasma volume.²¹ Testosterone, the key hormone of male sexual maturation, increases muscle mass, the main component of fat-free mass.¹⁷ Additionally, testosterone may increase the volume of total body water,¹⁷ possibly via its ability to directly stimulate sodium and water reabsorption in the proximal tubule of the kidneys.²²

A positive relationship of BP to fat mass has been observed many times previously. Obesity is a well-established risk factor for hypertension in both girls and boys.²³ Body fat relates positively to insulin resistance that, in turn, has been implicated in the development of hypertension.^{24,25} Insulin resistance also had a positive association with BP in our study. Some studies have reported statistically significant positive correlations between blood pressure and insulin, which has a strong correlation with insulin resistance²⁶ in adolescence,^{27,28} while oth-

ers have observed that the relationship is absent during this period of development.²⁹ The girls in our study, compared with boys, demonstrated both higher fat mass and higher insulin resistance. Fasting insulin, which has a strong correlation with insulin resistance (HOMA),²⁶ has been shown to be greater in female than in male adolescents in most,^{26,30,31} but not all, studies.²⁸ In adults, men have higher HOMA than women until HOMA values are adjusted for waist circumference (an index of intra-abdominal fat), at which point women have higher adjusted HOMA levels than men.³²

Intra-abdominal fat demonstrated a positive association with systolic BP that was greater in boys than girls. Intra-abdominal fat relates positively to sympathetic nervous system activity,³³ which, in turn, may contribute to the elevation of BP through its effects on vasculature and renal handling of sodium and water.^{23,34} The association of systolic BP with intra-abdominal fat observed to a greater degree in boys than girls here is consistent with our previous study in adolescence demonstrating that high levels of intra-abdominal adiposity are associated with higher BP in boys, but not in girls, and that this may be related to increased sympathetic activity also observed only in boys.⁴

In this large-scale study of healthy adolescence, we used a Finometer to measure hemodynamic parameters. The Finometer is a reliable device for tracking BP in adults and children older than 6 years,³⁵ but its accuracy to assess absolute values of stroke volume has come under question.³⁶ Nevertheless, it has been argued that the relative values are useful, particularly when invasive methods are not an option,³⁷ as they provide reliable measurements of stroke volume changes during various challenges. Thus, the Finometer has been shown to quantify aortic flow correctly from noninvasive BP measurement during orthostatic challenge.³⁸ Furthermore, the values of stroke volume obtained in the current study are similar to those obtained previously in 12- to 17-year-olds using noninvasive echocardiography. Echo-derived stroke volume has been shown to provide clinically acceptable estimates of stroke volume and to be as reliable as single-plane angiography for predicting stroke volume by thermodilution.^{20,39}

In summary, the results of the current study demonstrate that, in adolescence, BP is lower in girls than in boys at rest and during physical and mental challenges. This sex difference is closely related to sex differences in body composition and the relationships of individual body compartments to BP.

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